gial expansion. Glomeruli demonstrated pronounced granular staining with prominent IgA deposition.

- Murray and colleagues described the case of a patient with crescentic glomerulonephritis that developed 2 weeks after a $\beta$-hemolytic streptococcal throat infection and 33 days after streptokinase therapy for myocardial infarction.[29] They postulated that the previous sensitization by the streptokinase facilitated the hypersensitivity reaction to the streptococcal infection.

Retroperitoneal hematoma induced by streptokinase may press and obstruct the ureters, as may massive hematuria and blood clots.[30]

## Conclusion

Acute renal failure following streptokinase therapy for acute myocardial infarction is a relatively rare complication of thrombolytic therapy. The cause may be related to the infarction itself or to special effects of the streptokinase. When the disease is progressive, a renal biopsy may occasionally be indicated for diagnosing potentially treatable glomerular disease such as rapidly progressive glomerulonephritis.

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# Acute Leukemia Associated With Mediastinal Germ Cell Tumor

## De Novo Versus Therapy-Related Leukemia

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AGGRESSIVE MULTIMODALITY treatment of malignant diseases has resulted in a pronounced improvement in survival and even cure in patients with different types of cancer, such as Hodgkin's disease, non-Hodgkin's lymphoma, and germ cell tumor. The problem of secondary malignancy is of concern, however. An increase in the incidence of acute leukemia, predominantly myeloid type, is noted in patients who are cured of a primary malignant lymphoma, ovarian carcinoma, or germ cell tumor. The association of germ cell tumor with acute leukemia has been described.[1-4] We report a case of trisomy 8 acute monocytic leukemia occurring 20 months after the diagnosis and treatment of mediastinal germ cell tumor. We discuss the possible causes of the association between germ cell tumor and acute leukemia and the use

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of cytogenetic studies in the diagnosis of therapy-related leukemia.

### Report of a Case

The patient, a 23-year-old man, presented initially in September 1986 with general malaise, fever, and dry cough for three weeks. A chest x-ray film showed an anterior mediastinal mass with a secondary deposit in the lingular lobe of the left lung. A thoracotomy was done with excision of the mediastinal mass and wedge resection of the lingular lobe. The histologic diagnosis was nonseminomatous mixed germ cell tumor with elements of endodermal sinus tumor and embryonal carcinoma. A preoperative $\alpha$-fetoprotein level was not available, but a postoperative level was more than 800 $\mu$g per liter (800 ng per ml), and an assay for the $\beta$-human chorionic gonadotropin was negative. He was subsequently referred to our unit for further management.

On physical examination on referral, both testicles appeared normal. A computed tomographic (CT) scan of the abdomen showed normal-sized liver, spleen, and retroperitoneal lymph nodes. There was no intra-abdominal mass. The $\alpha$-fetoprotein level rose to 38,090 $\mu$g per liter. A regimen of cisplatin, 120 mg per m$^2$ of body surface, and etoposide (VP-16-123), 100 mg per m$^2$ for five days every two to three weeks, was started. The $\alpha$-fetoprotein level dropped to normal after three courses of chemotherapy. After the fifth course of chemotherapy, however, a solitary nodule appeared in the right upper lung field, and the patient had repeated episodes of septicemia. A right upper and middle lobectomy was done in March 1987. On histologic examination, the mass showed empyema with a thickened fibrous wall. There was no evidence of residual disease. Two more courses of cisplatin and etoposide were given after the operation, with a total cisplatin dose of 840 mg per m$^2$ and the total etoposide dose of 3,500 mg per m$^2$.

The patient attended for regular follow-up visits and had follow-up CT scans performed every three to four months with no evidence of recurrence. He was asymptomatic until April 1988, when a small suprapubic skin abscess developed. The leukocyte count was found increased to $102 \times 10^9$ per liter with 0.85 immature monocytes and 0.03 blasts, a hemoglobin level of 107 grams per liter (10.7 grams per dl), and a platelet count of $21 \times 10^9$ per liter. On physical examination, he had low-grade fever, hypertrophy of the gums, and shotty cervical lymph nodes. The liver and spleen were not enlarged. A bone marrow examination confirmed the diagnosis of acute monocytic leukemia, French-American-British classification M5b, with immature monocytes and blasts constituting about 45% of the nucleated cells in the marrow. Both erythropoietic and megakaryocytic series were markedly depressed. Cytogenetic study of the bone marrow aspirate showed trisomy 8 as the sole abnormality. The serum lysozyme level was elevated to 9,000 units per ml. The $\alpha$-fetoprotein level remained normal. Induction chemotherapy was given in May 1988 consisting of an infusion of cytarabine, 100 mg per m$^2$ per day for seven days, daunorubicin hydrochloride, 50 mg per m$^2$ per day for three days, and etoposide, 75 mg per m$^2$ per day for seven days. The disease, however, was refractory to the treatment, and the patient died of uncontrolled leukemia in June 1988.

### Discussion

Both leukemia and germ cell tumor are rare diseases, and the development of leukemia following germ cell tumor is unlikely to be coincidental. The leukemia more likely developed as part of the natural history of germ cell tumor or was therapy related.

There is evidence suggesting that malignant tumors may arise from different components of germ cell tumor.[5] The most frequent histologic type of such tumor is embryonal rhabdomyosarcoma, followed by nephroblastoma, chondrosarcoma, and adenocarcinoma. Similar events may have occurred for leukemia. Larsen and coworkers have reported the case of a patient with mediastinal germ cell tumor who was treated with chemotherapy followed by the resection of residual mediastinal tumor.[6] The resected tumor contained a population of mononuclear cells with the histologic features of lymphoblasts. Three months later, acute lymphoblastic leukemia developed. It was suggested that the lymphoblastic leukemia originated from the mediastinal germ cell tumor. Chaganti and Ladanyi and associates also reported the cases of three patients with mediastinal germ cell tumor in whom acute nonlymphocytic leukemia subsequently developed.[7,8] The authors were able to demonstrate the presence of isochromosome i(12p) in all the primary tumor and leukemic clones, suggesting the leukemia was derived from primary germ cell tumor. Oosterhuis and colleagues, however, could not confirm this finding in their patient.[9]

In a review of the literature, 30 patients had the development of leukemia simultaneously with or subsequent to a diagnosis of germ cell tumor, of whom 13 had mediastinal germ cell tumor.[1] When these data are compared with the fact that mediastinal germ cell constitutes only 1% to 5% of all germ cell tumors in humans, it is not difficult to appreciate the particular tendency of patients with mediastinal germ cell tumor to have acute leukemia develop after treatment. Recent follow-up studies further confirm the association of malignant hematologic disorders, especially acute megakaryocytic leukemia and malignant histiocytosis, with mediastinal germ cell tumor.[10] Nichols and co-workers postulated that the anatomic location within mediastinum might confer a particularly favorable microenvironment or growth factors may be elaborated, causing the malignant transformation of the multipotential germ cell within the tumor.

An adverse effect of chemotherapy is the other possible mechanism for the association of acute leukemia and germ cell tumor. It is known from studies of animals that cisplatin is both mutagenic and carcinogenic.[11] There have been several reports of cisplatin therapy-related leukemia occurring.[12-15] One of the authors also had a patient with small-cell carcinoma of the lung who was treated primarily with cisplatin and etoposide. The patient died four years later of therapy-related myelodysplasia transforming to acute myeloid leukemia with multiple karyotypic abnormalities and without any clinical evidence of primary small-cell lung carcinoma.

Etoposide therapy has also recently been implicated in therapy-related leukemia.[16-20] Recent data by Pedersen-Bjergaard and co-workers suggested an increased risk of myelodysplasia and leukemia after receiving etoposide, cisplatin, and bleomycin for germ cell tumor.[17] In their report, four cases of acute myeloid leukemia and one case of myelodysplasia occurred in a cohort of 212 patients with germ cell tumors treated with etoposide, cisplatin, and bleomycin. No leukemia was detected in a cohort of 127 patients previously treated with cisplatin, bleomycin, and vinblastine. The leukemia risk was also dose-related with no leukemia observed in those receiving a cumulative etoposide dose of less than 2,000 mg per $m^2$. Three leukemic patients had balanced chromosome translocation involving bands 11q23 or 21q22, which are characteristic for leukemia and myelodysplasia following treatment with etoposide. Pui and associates recently also showed that children with acute lymphoblastic leukemia who were treated with etoposide were at a higher risk of secondary acute myeloid leukemia developing.[19] They further showed that this risk is strongly associated with a weekly or twice-a-week dosing schedule.[20] Hence, there is no doubt that the chemotherapy commonly used for germ cell tumor can induce leukemia.

Therapy-induced leukemia, especially after the use of alkylating agents, is usually characterized by the presence of an antecedent hematologic disorder or a preleukemic phase, a trilineage dysplasia, frequent cytogenetic abnormalities, an ominous prognosis, and a poor response to antileukemic therapy.[21-24] The time interval from the initial treatment to the development of secondary leukemia or myelodysplasia is highly variable, ranging from several months to more than 20 years, with a median interval of five to six years. Those cases associated with etoposide therapy are typically without preceding myelodysplasia and with a short latency period.[16] The time interval from the initial treatment to the development of leukemia is not a useful index to distinguish de novo leukemia from therapy-related leukemia. A more reliable diagnostic tool is a cytogenetic study. Chromosome numbers 5 and 7 abnormalities are often seen in patients with therapy-related leukemia after receiving alkylating agents and chromosome 11q23 or 21q22 rearrangement in leukemia after the use of epipodophyllotoxins such as etoposide. Trisomy 8 is found in 36% of patients with acute nonlymphocytic leukemia. It also was seen more frequently in patients with leukemia associated with a previous malignant neoplasm or cytotoxic therapy.[22,25-27] In the 1990 article from Nichols and associates, trisomy 8, −5, and −7 were present in four of ten patients with hematologic malignant disorders and mediastinal germ cell tumors and in whom cytogenetic studies were done.[10]

Whether our patient's leukemia was therapy-related or de novo is difficult to establish. The relatively short interval between the treatment of germ cell tumor and the occurrence of leukemia did not exclude the possibility that it was related to the chemotherapy. On the contrary, it could be consistent with epipodophyllotoxin-induced leukemia.

With the evidence presented so far, the association of mediastinal germ cell tumor and hematologic cancer is well established. The mechanism of this association is far from clear, however. Our speculation is that a certain portion of the germ cell tumor contains a possible leukemogenic clone that manifests itself only when the patient survives long enough or that this leukemogenic clone is particularly susceptible to a leukemia-inducing effect of chemotherapy. The particular tendency for leukemia to develop in patients with primary mediastinal germ cell tumors may indicate a certain permissive role played by the mediastinum probably by the elaboration of appropriate growth factors. The association with the extremely rare acute megakaryocytic leukemia is interesting and unexplained. Detailed cytogenetic studies should be done on all patients with germ cell tumors, especially mediastinal. These patients should be observed closely for any occurrence of hematologic cancer so that appropriate cytogenetic and cell culture studies can be done promptly.

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# Severe Angioedema and Respiratory Distress Associated With Lisinopril Use

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ANGIOTENSIN-CONVERTING ENZYME (ACE) inhibitors are frequently used as first-line agents for the treatment of hypertension. Angioedema is a recognized but infrequent adverse effect of therapy, with a reported frequency between 0.1% and 0.2%.[1] Slater and co-workers analyzed 177 cases of angioedema associated with the use of enalapril maleate.[2] These cases were identified during clinical trials and postmarketing surveillance studies and from spontaneous reports of adverse reactions during postmarketing use. Of these 177 cases, 38 (22%) were classified as life-threatening, with patients having respiratory symptoms that included dyspnea, laryngeal swelling, laryngospasm, or stridor. Only 4 of the 177 patients (2.3%) required intubation, and all survived their episode of angioedema. Thus, severe angioedema producing respiratory compromise is rare (0.2% × .22) with an incidence of 0.044%, or 44 cases per 100,000 patients. Severe angioedema requiring intubation is extremely rare (0.2% × .023) with an incidence of 0.0023% to 0.0046%, or 2.3 to 4.6 cases per 100,000 patients. Most episodes occur within the first week after starting therapy but have been reported to occur as long as two years after the initiation of therapy.[3-9]

(Soo Hoo GW, Dao HT, Klaustermeyer WB: Severe angioedema and respiratory distress associated with lisinopril use. West J Med 1993 Apr; 158:412-417)

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Although experience with lisinopril, one of the newer nonsulfhydryl-containing ACE inhibitors, is limited, the incidence of angioedema associated with its use should parallel that of other long-acting agents such as enalapril and should also be about 0.2%. Over the past 21 months, we have been involved with the management of four patients in whom severe upper airway angioedema with or without respiratory distress developed associated with lisinopril therapy. Three of these patients required intubation for airway management. This represents a notably higher incidence of severe angioedema than expected from experience with other ACE inhibitors. The following report summarizes our experience with these cases.

## Report of Cases

### *Case 1*

The patient, a 50-year-old man with a history of asthma, long-standing hypertension complicated by end-stage renal disease requiring hemodialysis three times a week (baseline serum creatinine level, 486 μmol per liter [5.5 mg per dl]), and β-lactam antibiotic hypersensitivity, presented with massive tongue angioedema. He has had oropharyngeal edema associated with cephradine therapy that did not require intubation and that resolved with the administration of steroids and drug cessation. Over the past year and a half, his blood pressure control regimen included captopril and then enalapril. Two months before admission, lisinopril, 10 mg daily, was substituted for enalapril.

On the morning of admission, the patient took his usual medications: lisinopril, 10 mg; theophylline, 300 mg; and calcium carbonate, 4,800 mg. About two hours later, he noted swelling of his tongue. There was no pruritus, dyspnea, stridor, or associated symptoms. The similarity between this episode and the cephradine-associated angioedema prompted the patient to seek medical attention. In the emergency department, where he had progressive lingual edema and increasing difficulty with articulation, he was intubated. On physical examination after intubation, he had a blood pressure of 190/100 mm of mercury with a heart rate of 104 beats per minute and massive angioedema localized to the tongue, excluding the lips and the rest of the face (Figure 1); there were scattered urticarial lesions on the body, but the lungs were clear to auscultation. Before intubation and with the patient breathing 50% oxygen by face mask, arterial blood gas measurements showed a pH of 7.31, a $Pa_{O_2}$ of 153 mm of mercury and a $Pa_{CO_2}$ of 37 mm of mercury. A leukocyte count was $6.9 \times 10^9$ per liter (6,900 per μl) without eosinophilia. Complement C3, C4, and total complement levels determined three days after admission